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Amebiasis

GORDON McHARDY
WILLIAM W. FRYE

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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Amebiasis

GORDON McHARDY
WILLIAM W. FRYE

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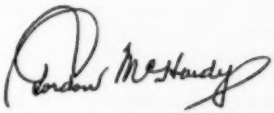
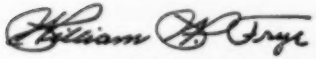


is a graduate of Tulane University School of Medicine. Following an internship in pathology, he received postgraduate training in internal medicine at the University of Rochester, Tulane University and Touro Infirmary. As Associate Professor of Clinical Medicine at Louisiana State University, he has continued his interest in graduate and postgraduate teaching in gastroenterology. His principal contributions to the medical literature have been in this field and reflect his interest in the clinical aspects of amebiasis.



received his Ph.D. degree from Iowa State University and his M.D. degree from Vanderbilt University School of Medicine. Since 1949, he has been Dean and Professor of Tropical Medicine at Louisiana State University School of Medicine and Head of the LSU Unit of the Charity Hospital at New Orleans. He has published more than 70 scientific articles and is a member of numerous medical and scientific organizations.

Drs. McHardy and Frye will moderate the panel on amebiasis for the World Congress of Gastroenterology in 1958.

DEFINITION

AMEBIASIS may be defined, for clinical purposes, as human infection with *Entamoeba histolytica*. Although implied, tissue invasion is not essential to the definition. In only one other amebic species, *Dientamoeba fragilis*, is tissue invasion a potential danger.

Descriptive terms that depict the various phases of amebic infection are: asymptomatic cyst passer, carrier state, asyndromic amebiasis, amebic diarrhea, amebic dysentery, amebic hepatitis, amebic abscess and amebic granuloma (ameboma). These will be described separately. We prefer to classify the

diarrheal states according to the type and severity of colitis rather than under the symptomatic title of diarrhea or dysentery.

The clinical material presented in this study represents amebiasis as it is seen in North America today. Amebiasis of the past, experiences with this disease in truly tropical areas and amebic involvement in the nutritionally depleted person or in the victim of prison compounds all represent disease states entirely at variance with that encountered in clinical medicine in the United States.

HISTORY

Losch's description, in 1875, of a fatality from amebic dysentery, identification of the offending parasite and attempt at reproduction of experimental amebiasis introduced the clinical concept of the disease (1, 6, 37, 42). Clinical knowledge of amebiasis in America gathered impetus from Osler's case study of hepatic involvement in 1890. The following year, Councilman and Lafleur published their classic analysis of 15 cases of amebiasis, coined the descriptive terms "amebic dysentery" and "amebic abscess of the liver" and established the clinical status of amebiasis. The contributions of Quincke and Roos, Schaudinn, Harris, Huber and Walker toward elucidation of amebic pathogenicity, differentiation of the organism, recognition of the cystic stage and animal experimentation culminated in experimental human infection by Musgrave and Clegg in 1905 (1, 6). Ingestion of cysts of *E. histolytica* by human volunteers, with reproduction of amebiasis, conclusively incriminated *E. histolytica* and exonerated *E. coli* in the experiments of Walker and Sellards in 1913. Because of the pathogenicity of *E. histolytica* and *D. fragilis* and the necessity for and difficulty in their differentiation from other harmless amebic commensals infecting human subjects, the cytologic studies of Dobell, which led to conclusive identification and classification, are of historic import (1, 6).

The significance of the cultivation work by Boeck and Drbohlav in 1925 can be ascertained by a review of the knowledge gained regarding amebiasis since that occasion. Through the notable contributions of Cleveland and Collier, Frye and Meleney, Dobell, Shaffer, Phillips, Balamuth, Rees,

and others to culture technic, amebae can now be cultivated in bacterial-inhibited and bacterial-free cultures. Knowledge of the life cycle, improved diagnostic methods, data on growth requirements and metabolism and in vitro therapeutic evaluation of potential amebacidal action of various agents have all contributed to our present knowledge of amebiasis. To complete the story, future investigators must determine the possible commensal status of *E. histolytica*, the requirements for pathogenicity, the factors that contribute to invasiveness and embolic (or metastatic) behavior, the causes of therapeutic intractability, better serologic and cytologic diagnostic aids and less toxic and more effective therapeutic measures.

ETIOLOGY

E. histolytica and, more rarely, *D. fragilis* are the only proved etiologic agents for human amebiasis. In general, *E. histolytica* is considered synonymous with amebiasis but must be differentiated from the other four harmless commensals that inhabit the large intestine of man but cause no damage to the tissues. *E. histolytica* exists in two well-defined forms, the trophozoite, or motile form, and the cyst (Figs. 1 and 2). The trophozoite is the active, growing, multiplying stage that may invade the tissues and produce lesions. It cannot live for any length of time away from the host. The cystic form of the ameba is able to survive in the external environment. The typical features of the cyst and trophozoite of this organism that permit identification are shown in Figures 1 and 2. Whereas these organisms are always potentiators of insidious, acute or chronic severe disease, they may, under certain circumstances, behave as temporary habitants of the intestinal tract or perhaps harmless commensals.

GEOGRAPHIC DISTRIBUTION

Amebiasis is no longer considered a disease confined exclusively to the tropical and subtropical regions. Its true incidence is not determinable by present modes of survey. Throughout the world, a large reservoir of infected persons exists who appear to be normal and have no intestinal symptoms at all. There is little correlation between the incidence

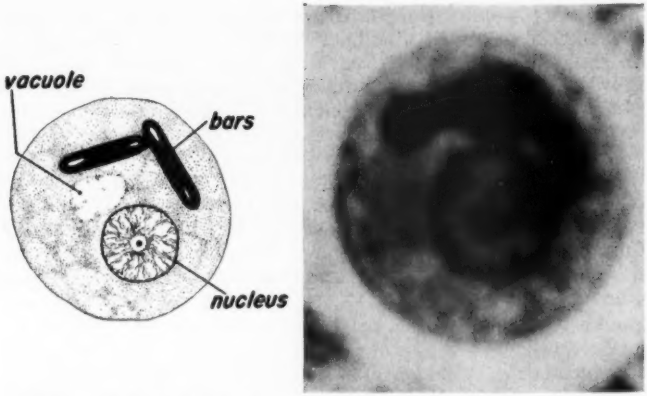


FIG. 1.—Typical *E. histolytica* (iron-hematoxylin stain) with characteristic nuclear structures (centrally placed karyosome) and blunt-ended chromatoid bars, with structural identification in sketch.

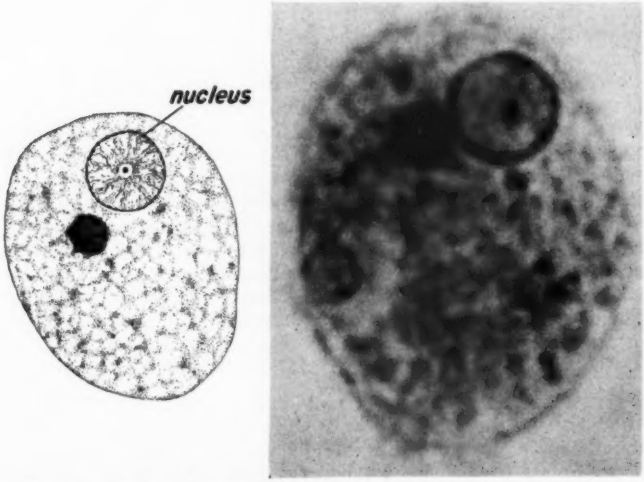


FIG. 2.—Typical *E. histolytica* trophozoite (iron-hematoxylin stain) with sketch depicting nuclear structure and an ingested erythrocyte.

of these so-called symptomless carriers and the relatively low frequency of acute amebic dysentery. Figures reported in publications vary directly with the intensity of interest in the disease (1, 2, 7, 23, 41). In a compilation from a series of surveys, Beltran (2) estimated global incidence to be 13%; to Europe he accredited 10%, to the Americas 12%, to Asia 16% and to Africa 17%. Craig and Faust (7) have been quoted as estimating the prevalence rate in the United States at 10%. From a review of selected published surveys in 1940, they obtained an incidence of 8.1%. Anderson and associates

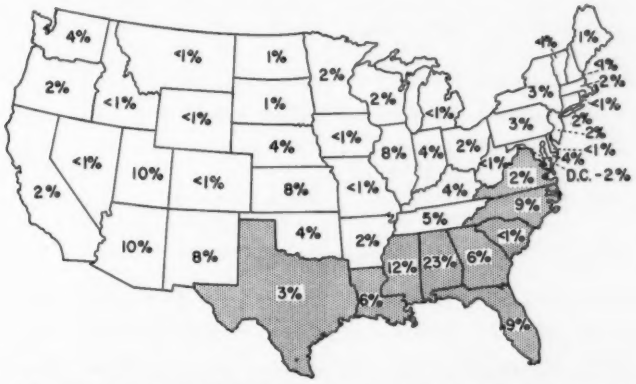


FIG. 3.—Average incidence per state obtained from survey of literature and questionnaire.

(1) gathered figures to justify a rate of occurrence of 9.96%, whereas Seneca's compilation resulted in an incidence of 8.1% for the United States.

The reviewer of these references will be pleased with the historic value of the studies, most of which predate our present-day public health preventive measures and therapeutic achievements. Predominantly, the data are derived from specialized studies on restricted populations, such as military confines, prison compounds, orphanages and mental hospitals. Obviously, such statistics do not represent a cross-section of our American population. Furthermore, in many cases an unusually high reported incidence may be inter-

TABLE 1.—RESULTS OF SURVEYS OF THE INCIDENCE OF ENTAMOEBA HISTOLYTICA INFECTION IN DIFFERENT POPULATION GROUPS IN THE UNITED STATES

YEAR REPORTED	AREA	REPORTED BY	TYPE OF PATIENT	NUMBER EXAMINED	PER CENT POSITIVE
1932	Tennessee	Meleney *et al.*	Rural population	20,237	11.4
1940	Missouri	Tsuchiya *et al.*	Medical and dental students	562	2.1
1941	Mississippi	Nickel	State laboratory specimens	49,170	4.4
1941	Oklahoma	McMullen *et al.*	Rural population	924	10.0
1942	Louisiana	Faust	College students	181	8.3
1942	Kentucky	Headlee *et al.*	College students	2,393	5.0
1945	New York	Birnkrant *et al.*	Well persons	1,822	6.8
1948	Tennessee	Anderson *et al.*	Hospital patients and personnel	246	17.0
1950	Wisconsin	Lincicone *et al.*	College students	1,110	3.5
1952	Louisiana	Hood *et al.*	Charity hospital	16,891	4.1
1953	Indiana	Brooke *et al.*	Factory workers	114	4.4
1954	N. Carolina	Mackie *et al.*	Rural school children	1,934	6.1
1955	Louisiana	Frye *et al.*	Institution	1,034	29.0

preted, as Brooke (3) has suggested, as a problem of diagnosis rather than disease.

On the basis of statistics from publications of a recent decade and from clinical and teaching sources, we have arrived at an incidence of 4% for the United States. Obviously, this national average requires adjustment for various specific localities, as shown in Figure 3. In the southern coastal states, for example, the incidence is 7.5%, whereas in the states bordering Mexico, a frequency of 5.8% is found. Results of surveys of the incidence of *E. histolytica* in different states are shown in Table 1.

INCIDENCE OF COMPLICATIONS

The incidence of the principal complication, hepatic abscess, depends on either or both the incidence and control of intestinal amebiasis (6, 8, 9). Obviously, declining incidence and improved therapeutic measures have contributed to the progressive decline in this complication. Statistical publications often convey an erroneous impression, because of their source. Postmortem studies, for example, which are limited to advanced cases, may yield an incidence varying from 7.6 to 84.4% (8). Clinical studies, which are usually restricted to hospitalized cases, reveal a prevalence rate that varies from less than 1 to 25% (8), but these figures too are biased, since most patients with uncomplicated amebiasis are no longer hospitalized for therapy. Data derived from an over-all

TABLE 2.—COMPLICATIONS OF AMEBIASIS
(4.7% of 709 Cases)

Hepatitis	15	Subphrenic Abscess	2
Granuloma (medical 4, surgical 2)	6	Prostatic Abscess	1
		Perforation	1
Appendicitis	6	Pleural Effusion	1
Hepatic Abscess	5		

From Browne, D. C., McHardy, G., and Spellberg, D. C.: Statistical evaluation of amebiasis, Gastroenterology 4:154, 1945.

TABLE 3.—COMPLICATIONS OF INTESTINAL AMEBIASIS

Intestinal Amebiasis	
Perforation	3
Hemorrhage	1
Appendicitis	1
Perianal abscess	1
Liver abscess	77
Secondary to Liver Abscess	
Pleuropulmonary	4
Brain abscess	1
Cutaneous Amebiasis (Unexplained)	1
Intestinal Amebiasis Associated with Carcinoma of the Colon	3

From: Rives, J. D., Heibner, W. C., and Powell, J. L. (39)

evaluation of office, clinic and hospital patients show an incidence of 0.63% for hepatic abscess and 1.8% for hepatitis (5). These figures would certainly seem to be accurate, since the severity of this disease state precludes its remaining unrecognized.

The frequency of other complications in our experience is shown in Table 2 (5). From our surgical service the complications are tabulated in different relationship (Table 3). The progressive decline observed in all complications is probably attributable to decreased incidence of amebic infection, improved diagnostic facilities and better therapy.

EPIDEMIOLOGY AND TRANSMISSION

Although monkeys, dogs and rats have been found to be naturally infected with *E. histolytica*, these reservoir hosts are not considered to be an important over-all source of human infection. Epidemiologically, the reservoir of amebae for human infection is man himself. The presence of viable cysts in the human host constitutes a continuing chain of infection. Human infection results either from the swallowing of food or drink that contains viable cysts of *E. histolytica*, or by direct contact from man to man.

Flies and cockroaches that have had contact with fresh, infected feces may be responsible for contamination of food. It has been demonstrated in the laboratory by numerous workers that cysts of *E. histolytica* can pass through the intestinal tract of flies and cockroaches unharmed. These insects may be important transmitters of amebiasis when food is left unprotected. Infected food handlers who practice poor personal hygiene are often a major source of infection. When the food handler in the family is infected and is passing cysts of *E. histolytica* in the stools, a large proportion of the members of that family has been found to be infected. Thus, personal hygiene is an important factor.

Direct transmission of amebiasis may result from conditions of overcrowding or close contact such as those that prevail in mental or other institutions. Unprotected water supplies are likely to be heavily contaminated. Amebic cysts can survive for a considerable period in water or moist surroundings and under certain adverse climatic conditions. They may also survive in extremely low temperatures but are quickly killed by sunlight or drying and by heat.

The two major epidemics of amebiasis in a civilian population have occurred in the Great Lakes area, and careful studies revealed a contaminated water supply to be the most probable source of infection. A sewage-contaminated water supply was undoubtedly the source of the now famous Chicago hotel epidemic of 1933 (45). The epidemic in South Bend, Indiana in 1953 (22, 40) was restricted to the employees of a woodworking plant. Fecal examinations of all employees indicated that 52.4% of the 1,542 participants in the diagnostic program harbored *E. histolytica* in their gastrointestinal tracts. Careful epidemiologic, laboratory, clinical and therapeutic studies of this epidemic have been reported (22, 40). These water-borne outbreaks have demonstrated that contamination of public or private water supplies may be a major source of infection in a given population. Present methods of chlorination of water supplies to combat bacterial contamination are evidently not adequate for control of *E. histolytica* cysts.

PATHOLOGIC FEATURES

Amebic infection occurs by introduction of a cyst or cysts into the mouth of an uninfected host. The cyst passes unharmed through the stomach and enters the small intestine. During passage through the small intestine or after arrival in the cecum, excystation occurs, and trophozoites are released into the lumen of the intestine. In a favorable environment, the trophozoites may continue to multiply indefinitely. The motile amebae may remain in the lumen, without invading the tissue, and be carried in the fecal contents toward the terminal portion of the large intestine, simultaneously undergoing encystation in preparation for survival outside the body. Little is known about the conditions that determine the development of the cysts from the motile forms. Encystation does not take place in the tissues but only in the trophozoites in the lumen of the intestine.

If conditions in the cecum or other parts of the large intestine are favorable, the motile amebae may penetrate the wall of the intestine and produce tissue damage. Penetration into the tissues may be accomplished by combined physical and chemical action. Ameboid movements of the parasite may result in penetration between the epithelial cells. Trauma to these cells may permit invasion beneath the epithelium or,

by a lytic substance, the epithelium and other cellular structures may be destroyed. Usually, the amebae invade the epithelial cells and migrate to the base of the glands, where they multiply outside the basement membrane before perforating the connective tissue stroma of the mucosa. In many instances in which initial tissue invasion occurs, the lesions are limited to the mucosal layer and only superficial ulcers develop.

Often, the trophozoites invade the stroma superficially, gaining access to blood or lymph capillaries, through which they may be carried directly to the submucosa. In the submucosa, the amebae spread out in all directions. Their presence in this area causes edema, fibrin formation and degeneration of cells and intercellular fibers. There is little or no cellular response on the part of the host to the amebae, so that in early lesions, before bacterial contamination, few polymorphonuclear leukocytes and only a moderate number of mononuclear cells may be found. With progression of the amebic lesions, the bacteria gain access to the tissues, causing a severe polymorphonuclear response, and the degenerating lesion takes on the appearance of a pyogenic abscess. At the periphery of such a lesion, bacteria are usually absent, but numerous amebae are present in the area of advancing edema and necrosis. Development of such a lesion in the submucosa leads to interference with nutrition of the mucosa above and consequent formation of the so-called bottleneck ulcer, with extension of blood, necrotic material and amebae into the lumen of the intestine. Advancing beyond the area of necrosis, the amebae in the submucosa may enter the larger lymph or blood vessels or may penetrate through the muscular coat of the intestine and occasionally cause perforation into the peritoneal cavity. More frequently, irritation to the peritoneal surface, with resulting adhesions, ensues. If they enter the blood vessels, they are carried by the blood stream to the liver, where they cause necrosis of the capillary walls, and finally, with extension of this damage to the tissue, they form a hepatic abscess.

Distribution of Lesions in the Intestinal Tract

Most lesions occur in areas in which there is stasis of intestinal contents. Figure 4 shows the distribution of the le-

sions in the large intestine; the cecum and the sigmoid flexure are the most frequent sites of involvement.

The pathologic changes described represent the development of the most severe type of amebic lesion in the large intestine of man. In most infections, the initial lesion is limited to the superficial mucosal layer of cells, and only superficial ulceration develops. Rapid repair of the tissue may

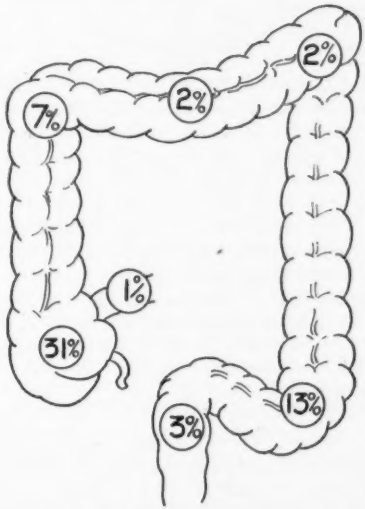


FIG. 4.—Relative single location frequency of gross amebic pathologic involvement (multiple sites of involvement in 41%).

thus keep pace with sloughing of the necrotic cells. In persons who have died of causes other than amebiasis, there may be no evidence of gross pathologic change, but microscopic lesions may be demonstrable in the tissue sections. In such lesions, the amebae may be present in the tissue without definite necrosis. Glandular epithelium may be absent in small areas but, except for the presence of trophozoites of *E. histolytica*, the surrounding tissue may exhibit little or no change. Such a condition represents either the presence of a strain of *E. histolytica* with a low degree of pathogenicity or

unusual resistance of the host to the parasite. Faust (10), in 1941, examined the intestinal tracts of 202 apparently normal healthy persons within 4 hours after accidental death. In 13 of these, cysts or trophozoites of *E. histolytica* were recovered from the large intestine, and in 7 of the 13, positive superficial lesions of varying extent were found. This study indicates that extensive amebic infection may exist in the large intestine without gross evidence of the disease.

PATHOGENICITY

The pathogenicity of different strains of *E. histolytica* has been studied by many investigators. Meleney and Frye (11-15, 30-35), from 1932 to 1938 carried out studies in kittens to determine the severity of the lesions produced by the different strains and to observe the effect of continuous, prolonged cultivation and other measurable factors on the pathogenicity of the different strains of this organism. These controlled studies, which included a standard number of experimental animals in each group, demonstrated differences in the ability of various strains to produce lesions in kittens; these could be shown to be constant over a period of years. None of the strains of *E. histolytica* used in these studies proved to be nonpathogenic in the kitten.

The large and small races of *E. histolytica* have been considered by some to account for the variable clinical manifestations of the disease in man. Many clinicians believe that the small race is less pathogenic and produces fewer symptoms than the large race. Frye and Meleney (15) established a small race of *E. histolytica* in culture from a patient with mild gastrointestinal symptoms and tested its pathogenicity in a series of experimental animals. Cultures of this strain were inoculated into 22 kittens, 5 of which became infected. The lesions in the animals were superficial, with little tendency for the amebae to penetrate deep into the tissues, in contrast to the deep penetration of almost all the large strains similarly studied in kittens. Whereas it is not possible to transfer such information directly to the human subject, these observations suggest that this strain may produce only superficial, if any, signs or symptoms of the disease in man.

Jones and associates (20) recently reported results of a controlled linear study of amebiasis in nondysenteric and mild hepatic forms of the infection in Egyptians. Little is

known of the natural history of human amebiasis, and no precise data are available from long-range serial clinical and laboratory studies of untreated persons harboring small or large race of *E. histolytica*. Jones and co-workers organized a carefully controlled "double blind" clinical and laboratory study on 19 "apparently healthy" Egyptians during a pretreatment period of 24 weeks. Ten of these 19 persons were infected with varying frequencies and densities of both the large and small races, 5 with small race only, and 4 had persistently normal stools. According to medical records in their place of employment, none of these persons had sought treatment for diarrhea or dysentery during the previous year. Those harboring both the large and small races of *E. histolytica* had a distinctly higher frequency of abnormal stools, flatulence and abdominal cramps than did either those with small race infections alone or the controls. Abdominal signs were about 7 times more frequent in the patients with mixed and small race infections than in the control group without infection. These observations were interpreted as clinical support for the concept of mild pathogenicity of the small race and for the belief that "apparently healthy carriers" of either race, if followed over a long enough period, may be found to have mild symptoms and signs of amebiasis.

Extraintestinal Amebiasis

Extraintestinal lesions caused by *E. histolytica* are metastatic or extensions derived primarily from lesions in the intestinal tract. In the most common and important complication of amebiasis, amebic hepatitis or amebic abscess of the liver, the amebae are transported from the intestinal lesions to the liver by way of the portal blood stream. With superficial localization of the hepatic abscess, its extension to the surface of the liver is the rule, and adhesions to the adjacent viscera or parietal peritoneum are common, often resulting in perforation or direct extension outside the liver.

The next most important site of extraintestinal amebiasis is the lung. Such lesions may occasionally be embolic in origin but are usually caused by direct extension of hepatic abscesses through the diaphragm. The abscess may rupture into the pleural cavity, but, more often, the lung becomes adherent to the diaphragm and extension occurs directly into the lower lobe. With the advance of the amebae into the lung,

localized pneumonia develops, with rapid formation of an abscess. The pulmonary abscess usually opens into a large bronchus, discharging into the sputum a brownish mucoid material that contains blood and amebae. If the direct connection with the liver remains, the discharge is similar to that of a hepatic abscess. At the periphery of the abscess develop-

TABLE 4.—EXTRAINTESTINAL COMPLICATIONS

Organ or System Involved	*Type of Complication*
Liver	Hepatitis
	Liver abscess
	Subdiaphragmatic abscess
	Subhepatic abscess
Lung	Lung abscess
	Empyema
	Pleural effusion
	Pleuritis
	Bronchohepatic fistula
Cutaneous	Involvement of skin of abdominal and thoracic walls
	Perianal
	Anal
	Perineal
	Vaginal
Central Nervous System	Brain abscess
Heart	Amebic pericarditis
Genitourinary	Penile ulcers
	Urethritis
	Cystitis
	Pyelitis
	Kidney abscess
	Perinephric abscess
Spleen	Splenic abscess
Gallbladder	Pericholecystitis

From Browne, D. C., McHardy, G., and Spellberg, D. C.: Statistical evaluation of amebiasis, Gastroenterology 4:154, 1945.

ing in the lung there is a pneumonic process, partially interstitial in character but mainly showing the alveoli filled with fibrin and amorphous material containing few cells. Numerous amebae may be irregularly distributed in the alveoli and, to a lesser extent, in the interstitial tissue. In cases where the amebae gain access to the lung by way of the blood stream, the diaphragm may not be involved, and the origin of the abscess lies within the parenchyma of the lung.

Amebic lesions of the skin and subcutaneous tissues are frequently found. Such lesions may occur after surgical drainage of an amebic hepatic abscess, after drainage of a ruptured appendix, from a colostomy or from direct extension of rectal ulcers through the anus by way of a fistula. These need never occur if the primary condition is recognized and treatment is instituted.

Other extraintestinal amebic lesions have been reported, but these are extremely rare (Table 4). Amebic abscess of the brain is usually secondary to hepatic and pulmonary abscess. Amebic infections of the gallbladder and of various areas of the genitourinary tract have been described. When *E. histolytica* is found in these organs, it is undoubtedly due to an extension from a primary site in the liver, in case of the gallbladder, or from the colon, in case of involvement of the genitourinary tract.

DIAGNOSIS

Recognition that infection with *E. histolytica* may exist without active symptoms and in association with many diseases demands more than casual examination. The clinician must evaluate each case individually. Whereas the physician with many years of experience in the study of dysenteries can frequently make an accurate diagnosis of fulminating amebic or bacillary dysentery on the appearance of the freshly passed stool, this method does not provide a satisfactory diagnosis of either amebiasis or other forms of dysentery. The laboratory diagnosis of amebiasis is not particularly difficult but, like any other technical procedure, it requires some knowledge and experience. The clinical diagnosis of intestinal amebiasis is not difficult to confirm by present-day laboratory technics. Specific diagnosis of amebiasis depends on demonstration of either cysts or trophozoites of *E. histolytica* in the stool or in other exudates. Insofar as is practicable, methods designed to demonstrate the pathogenic amebae must be exhausted before a clinical or therapeutic diagnosis of amebiasis is accepted.

When symptoms suggestive of amebic infection persist or recur after adequate amebacidal therapy, other disease entities that may coexist or be causative must be considered. Tabulation of important concomitant enteric diseases is reproduced here to emphasize the importance of differential

diagnostic evaluation (Table 5) (11). In hepatic disease, neoplasm, hepatitis and pyogenic abscesses are the important differential diagnostic considerations.

Laboratory Diagnosis

Swartzwelder (43) has outlined in detail the necessary laboratory procedures for the diagnosis of amebiasis. Errors in diagnosis include: (1) failure, because of poor technic or inadequate search, to detect the organism in persons who harbor the parasite, (2) confusion of various nonparasitic objects in the stool or in sigmoidoscopic aspirate with *E. histolytica* (Figs. 5, *A* and *B*) and (3) confusion of other

TABLE 5.—Enteric Disease Concomitant with Amebiasis
(encountered in 709 cases)

Severe anal constriction	14	Benign polyposis	2
Proctitis (*nonspecific*)	11	Gonorrheal proctitis	2
Anal fissure	8	Endometriosis (*serosal implantation*)	2
Bacillary dysentery	8	Staphylococcal ulcerative colitis	1
Diverticulosis of colon	6	Cecal volvulus	1
Malignant disease of colon	6	Lymphogranuloma venereum	1
Chronic idiopathic ulcerative colitis	4	Ileocecal tuberculosis	1
Fistula-in-ano	3	Other enteric parasites	28

(Figs. 5, *C*–6, *C*) intestinal protozoa with *E. histolytica*. A fresh fecal specimen free from oil or barium, proper smear technic and methodical, thorough search for amebae are all essential for detection of intestinal amebae in direct fecal smears.

The probability of detecting amebiasis by various technics of fecal examination is demonstrated in Figure 7. For most efficient diagnosis of intestinal amebiasis, 3 or more fresh stool specimens and 1 fresh warm specimen obtained after saline purgation (unless diarrhea or dysentery is present), should be examined by direct smear and by one of the concentration technics. Both the direct saline smear and the iodine preparation should be used. Hematoxylin-stained film is useful for study of the detailed morphologic characteristics of the organisms. One concentration technic should always be used on every fecal specimen after examination of the

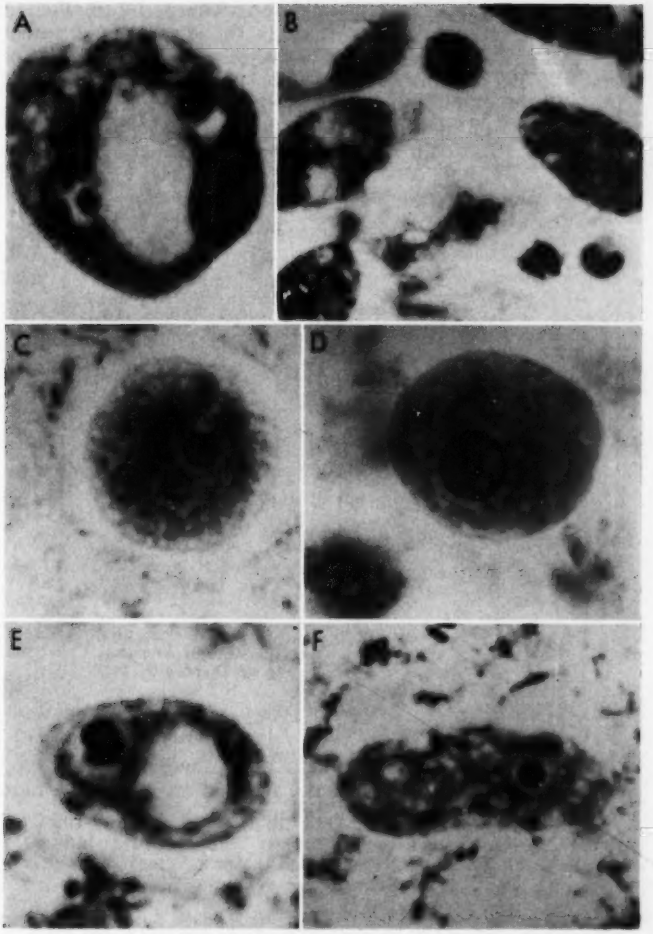


FIG. 5.—*A*, phagocytic artifacts; *B*, artifacts: phagocytes and neutrophites; *C*, cyst of *E. coli*; *D*, trophozoite of *E. coli*; *E*, *I. butschlii* cyst; *F*, *I. butschlii* trophozoite.

direct fecal smear. The zinc sulfate technic is more efficient for demonstration of cysts than is the direct fecal smear (43). All concentration technics are of value in detection of cysts but not of trophozoites. The formalin-ether technic (38), which is simple and not time-consuming, is excellent for detection and identification of protozoan cysts and helminthic ova of almost all intestinal parasites. Since it has been

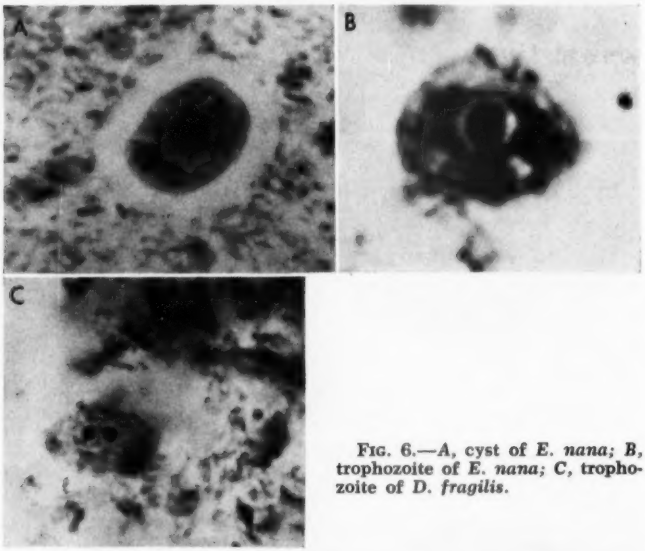


FIG. 6.—*A*, cyst of *E. nana*; *B*, trophozoite of *E. nana*; *C*, trophozoite of *D. fragilis*.

demonstrated to be both efficient and practical in the diagnosis of amebiasis, details of the technic are presented here for use in a routine diagnostic laboratory (38).

FORMALIN-ETHER CENTRIFUGAL SEDIMENTATION TECHNIC FOR STOOL EXAMINATION

1. Fill 15 cc. centrifuge tube (*with conical base*) half full with tap water.
2. Place at least 2 cc. of feces in the water and mix well by means of wooden applicators. Fill the tube to within ½ inch of top with additional water and mix well.

3. Centrifuge at 1,500 r.p.m. for 2 minutes. Decant the supernatant fluid.
4. Add 10% formalin to the sediment until the tube is one half full; mix thoroughly, and *allow to stand for 5 minutes.*
5. Add about 3 cc. of ether (until tube is three fourths full); stopper the tube (or use thumb or rubber finger cot) and *shake vigorously; remove the stopper or thumb carefully* to prevent spraying of material due to pressure within the tube.

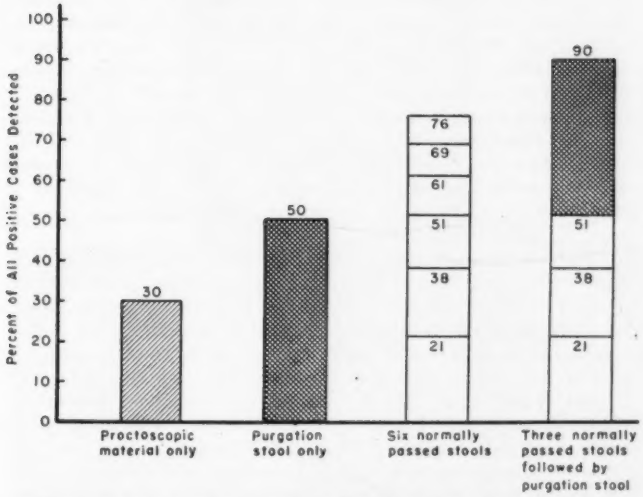


FIG. 7.—Relative probability of detecting amebiasis by various modes of obtaining diagnostic material. (Modified from W. G. Sawitz, *Medical Parasitology* [New York: Blakiston Div., McGraw-Hill Book Company, 1956].)

6. Centrifuge at 1,500 r.p.m. for about 2 minutes. Four layers should result: a small amount of sediment containing most of the parasites, a layer of formalin, a plug of fecal debris on top of the formalin and a topmost layer of ether.
7. Free the plug of debris from the sides of the tube, by ringing with an applicator stick, and carefully decant the top 3 layers.
8. Mix the remaining sediment with the small amount of fluid that drains back from the sides of the tube. Drag sediment from tube onto a fecal slide by means of applicators. Prepare iodine and unstained mounts of the sediments for microscopic examination.

Proctosigmoidoscopic Examination

Results of proctosigmoidoscopic examination may be entirely negative. In only 17.7% of 603 of our symptomatic cases were mucosal changes demonstrable (5). When present, however, such changes are of confirmatory value. Sigmoidoscopic examination is a particularly valuable diagnostic adjunct in patients in whom careful and repeated fecal examinations have failed to reveal amebae. It provides an additional means of obtaining diagnostic material for microscopic examination. Soapsuds enemas should not be used in preparation of the patient for sigmoidoscopic examination. Saline purgation or enemata are satisfactory. As shown in Figure 7, proctoscopic examination alone is most inefficient for diagnosis of amebiasis. Since lesions beyond the range of the instrument cannot be detected, many instances of amebiasis may be overlooked, especially when lesions are confined to the cecum, appendix and ascending colon, which are sites of frequent involvement.

A heavy-walled, smooth-tipped glass or metal tube is most suitable for obtaining material for microscopic examination; a cotton swab is not satisfactory for this purpose. The material aspirated from the lesions should be smeared into a drop of saline and examined carefully for typical motile amebae. Even if no definite lesions are observed, mucus and other material present in the lumen of the intestine should be examined primarily for trophozoites in the unstained saline smear. The only safe diagnosis of *E. histolytica* from unfixed and stained proctoscopic material is based on demonstration of a living, motile ameba, with the characteristic progressive movement of active trophozoites of *E. histolytica*. Diagnosis should never be attempted on rounded-up cells resembling trophozoites or possibly cysts, as the cysts are not usually observed in sigmoidoscopic aspirates. According to Hood, Sodeman and Akenhead (19), if a careful, competent study is made of the patient's stools, supplemented by freshly passed saline-purged or saline-enema specimens, proctoscopic material will usually provide a few additional cases of infection with *E. histolytica*.

The initial amebic ulceration is a minute, isolated, superficial, mucosal erosion with minimal circumferential erythema. This progresses to a pinpoint, petechial ulceration on the peak of a forming nodule that simulates a normal mu-

cosal lymphoid follicle. From the stoma can be expressed or aspirated sanguinopurulent material containing *E. histolytica.* Necrotic undermining, resulting from secondary infection, produces raised, irregular edges, which destroy the characteristics of the initial lesion. Only the presence of uninvolved

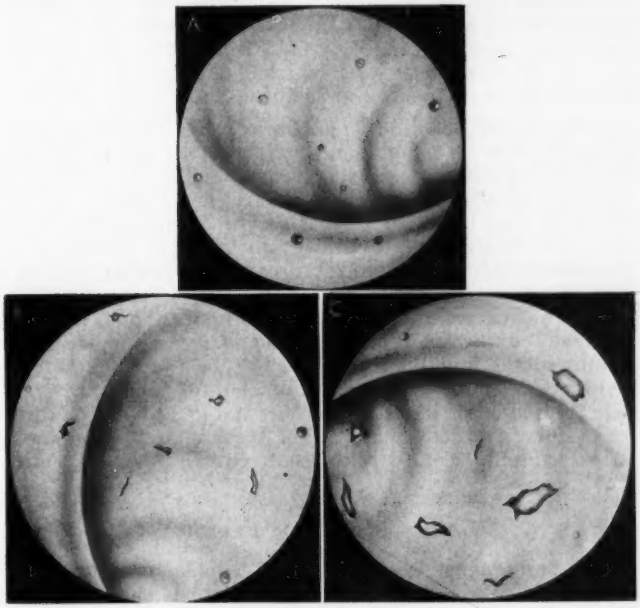


FIG. 8.—Proctosigmoidoscopically viewed amebic ulcerations. *A*, early minute petechial ulceration; *B*, necrotic undermined moderately advanced lesions; *C*, secondarily infected giant ulcers.

normal mucosa between lesions distinguishes amebic lesions from other forms of ulcerative colitis. Coalescence may produce giant ulcers. Healing may result in pale yellowish mucosa with a new lesion nearby. Lesions have been encountered in all stages of development that defy textbook characteristics (Figs. 8, *A-C*).

Granulomas appear, proctoscopically, as indurated nodules

with extensive superficial ulceration and sinuses that exude purulent material. On biopsy, the opened surface is a mixture of dense fibrous tissue, granulation and purulent necrosis. Often, biopsy precipitates a slough, which results in a large necrotic ulceration with a moundlike granular edge. Differentiation from neoplasm and from mycotic and other inflammatory granulomas depends on demonstration of *E. histolytica* and histologic elimination of other disease.

Cultures

Fecal specimens and sigmoidoscopic aspirates may be cultured for *E. histolytica* on a variety of media. It has been observed by many workers that some strains of amebae do not grow satisfactorily in the standard media (10a), and the diagnosis may be missed unless careful fecal examination is done simultaneously. Culture of stools for *E. histolytica* is, therefore, generally less efficient than fecal examination as a routine diagnostic procedure. Furthermore, results of the culture are delayed at least 24 to 48 hours. Thus, currently available cultivation procedures should never supplant fecal examination but may, in selected cases, be a profitable supplement. Swartzwelder (43) has found cultures particularly valuable for nonmotile large trophozoites not identifiable on direct fecal smears. Often, a culture of fecal material containing such forms has yielded a luxuriant growth of *E. histolytica*.

Immunodiagnostic Features

The immunologic technics now available for diagnosis of amebiasis are unreliable, and other methods should be used for intestinal amebiasis. The complement fixation test, which is the only one that has yielded any degree of success, may be of assistance in the diagnosis of hepatic amebiasis. The major difficulty, however, is that a reliable, potent, stable antigen is difficult to prepare. In the light of our present knowledge, its value as an aid in the diagnosis of amebiasis is difficult to assess. Various types of precipitin tests have been developed, none of which is reliable. There is a need for development of a reliable serologic test for amebiasis, not to replace, but to confirm, fecal examinations for *E. histolytica* and for use in cases of extraintestinal amebiasis, in

which it is frequently impractical to obtain material for microscopic examination. The Moan test is under continued but inconclusive evaluation at this writing.

Acquired immunity has been considered by some investigators to be responsible for the decline of incidence of amebiasis in the older age groups. All studies to date seem to disprove this assumption, there being no definite evidence of acquired immunity in man and little in experimental animals. Swartzwelder and Avant (44) reported that dogs which had recovered spontaneously or had been cured with drugs were extremely resistant to reinfection. Transfer of blood from immune animals seemed to confer some protection on the recipients. The fact that some experimentally infected animals may recover spontaneously, at least from the acute phase of the infection, suggests the acquisition of immunity, but the features of this recovery have not been analyzed. That spontaneous recovery takes place in human subjects has been assumed for many years. Martin and associates (29), in a study of the treatment of acute amebic dysentery, followed 66 patients who had had no specific therapy. At the termination of the follow-up period, 11 of the 66 patients had no clinical or parasitologic evidence of amebic infection and could, by the standards used, be considered successfully treated. In addition, 5 had recovered clinically but their stools still contained *E. histolytica*. This is the first report of a careful study of acute cases of amebic dysentery with spontaneous recovery and complete loss of the parasite without specific therapy. What immunologic or other factors were responsible for this recovery were not determined.

Diagnosis of Extraintestinal Amebiasis

The diagnosis of extraintestinal amebiasis consists of careful examination of aspirates and exudates as well as biopsies for trophozoites of *E. histolytica*. The organisms occur in the tissues only in the trophozoite stage, and cysts are found only in the lumen of the intestine. The most common site of extraintestinal infection is the liver. Specific diagnosis of amebic hepatic disease is often difficult; early hepatic involvement, with possible multiple foci, makes aspiration impractical. On the other hand, with later development of a large localizing hepatic abscess, roentgenographic examination may prove helpful. The chocolate color of the material

aspirated from such abscesses is usually considered pathognomonic of amebic infection. Since the amebae are located primarily in the wall of the abscess in living tissue, the trophozoites may not be found in the contents of the abscess. Culture technics for identification of *E. histolytica* in abscess material are not satisfactory. Specific diagnosis, in case of hepatic abscess, is usually difficult, and other methods of diagnosis must be relied on.

In cutaneous and all other forms of extraintestinal amebiasis, laboratory diagnosis can be made by biopsy or careful examination of the aspirates and scrapings for the presence of typical trophozoites of *E. histolytica*, both saline preparations and stained smears being used, if necessary. Cysts have never been found in such aspirates, as they do not develop in the tissues.

Differential Diagnosis

Numerous objects frequently confused with intestinal amebae include leukocytes, macrophages, oil droplets and *Blastocystis hominis*, which may closely simulate amebic cysts. Macrophages may be mistaken for trophozoites of *E. histolytica*. Even for the experienced laboratory worker, these cells are often difficult to distinguish from the pathogenic ameba. Many other objects may be found in the stool, in aspirates and in exudates, but the diagnosis of *E. histolytica* should never be made when the object can reasonably be interpreted as an artefact. According to Swartzwelder (43), the best rule for avoiding an erroneous diagnosis of nonparasitic fecal objects as *E. histolytica* is to make the objects meet the morphologic criteria of *E. histolytica*. Never alter the criteria for *E. histolytica* to meet the objects seen in exudates or other material because of enthusiasm for a diagnosis of amebiasis.

ROENTGENOGRAPHIC STUDIES

Roentgenographic evidence of amebiasis depends on the degree and type of involvement. In the early and acute stages of ulceration, the mucosal surface becomes irregular and fuzzy in outline, and there is associated spasm. Such changes have no specific diagnostic features. With progres-

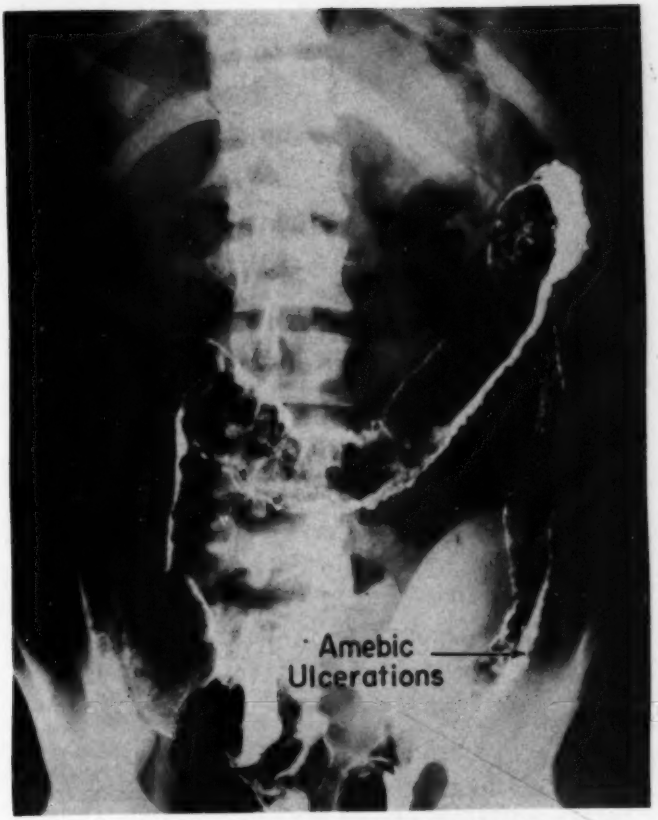


FIG. 9.—Diffuse serrations in proved amebic ulcerative change.

FIG. 10.—Conical cecal deformity with incompetent ileocecal valve.

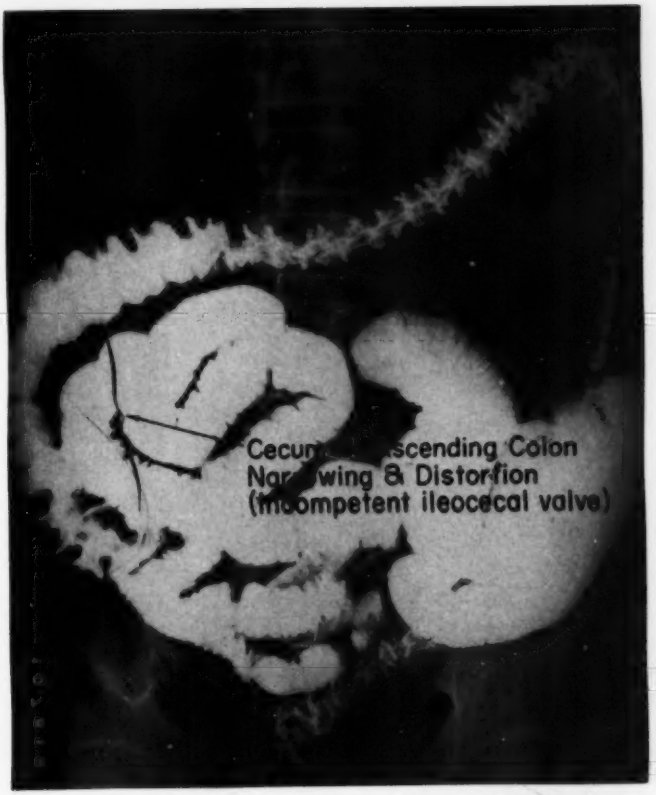


FIG. 11.—Diffuse cecal involvement with generalized colonic amebiasis.

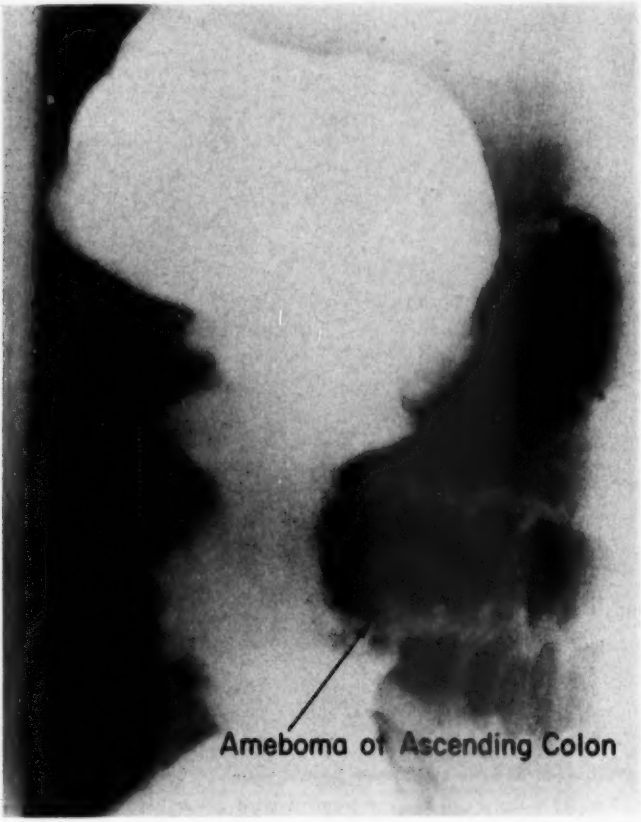


FIG. 12.—Amebic granuloma as space-occupying lesion.

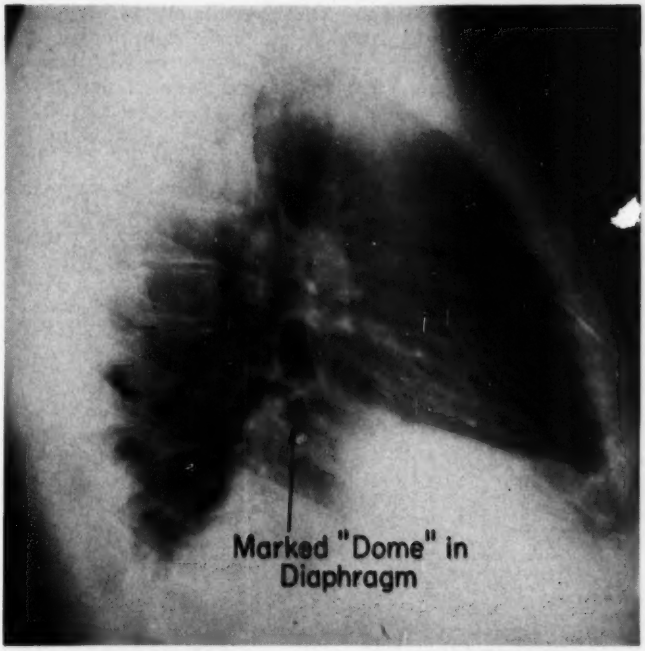


FIG. 13.—Right diaphragmatic deformity in amebic hepatic abscess.

sion, minute pinpoint serrations denote the ulcer craters. The mucosal outline appears shaggy, and the lumen narrows as the disease becomes infiltrative (Fig. 9). In *cecal involvement*, a typical conical contour characterizes the cecal tip, and the ileocecal valve often becomes abnormally patent (Figs. 10 and 11).

The space-occupying granuloma is difficult to differentiate from a neoplasm. It is most frequently single and cecal or sigmoid in location. Because of its refractoriness to therapy, the diagnostician has difficulty excluding the possibility of neoplasm even when *E. histolytica* is isolated (Fig. 12). Exacting therapy should always precede operation.

The roentgenographic appearance of *hepatic amebic ab-*

scess was relatively specific in approximately 44 (88%) of our 50 case studies (5). Involvement of the right hepatic lobe (in 84 to 86% of cases) is usually associated with characteristic elevation, distortion and disturbance in motility of the right diaphragm. The lateral film is expected to show, in addition to diaphragmatic elevation, obliteration of the

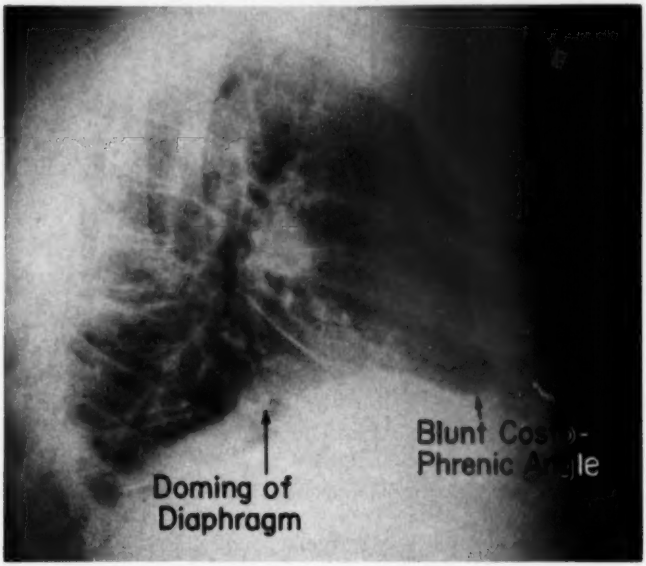


FIG. 14.—Right diaphragmatic deformity and blunting of costophrenic angle in amebic hepatic abscess.

anterior costophrenic angle (Fig. 13). The cardiophrenic angle is obliterated in the anteroposterior film. The diaphragm may be domed (Fig. 14). Pleural and pulmonary reaction may indicate right basal pneumonitis; effusion may confuse the picture.

If the abscess projects inferiorly, the gallbladder shadow will be low and the hepatic flexure of the colon may be depressed. Involvement of the left hepatic lobe, although

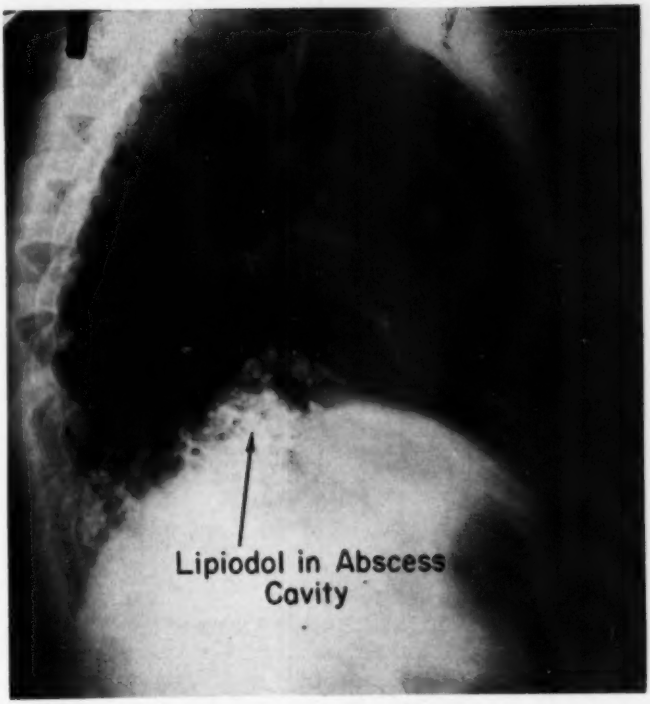
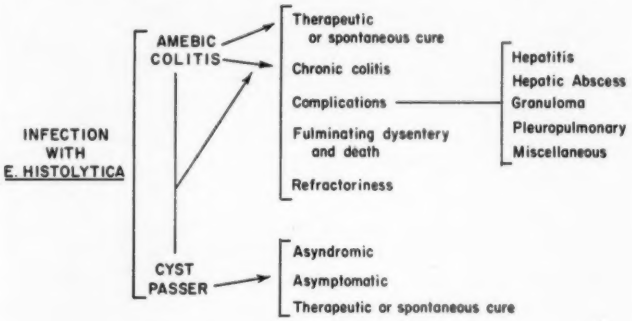


FIG. 15.—Intrabronchially administered lipiodol in hepatic abscess cavity.

rare, may create a crescentic pressure deformity of the lesser gastric curvature.

Hepatopulmonary involvement may be considered a progression of hepatic abscess. Pleuropulmonary involvement may be delineated by intrabronchial introduction of iodized oil and depiction of communication between the bronchial tree and a hepatic abscess (Fig. 15). Hepatography, pneumonoperitoneum and delineation of abscess cavity are adjunctive procedures employed only when the additional hazard is justified because of inconclusive findings.

TABLE 6.—Potential Clinical Manifestations of Amebiasis



CLINICAL MANIFESTATIONS

Amebiasis is not associated with any specific or characteristic symptoms. For clinical purposes, it is practical to divide this disease into its components. Its potential clinical manifestations, as observed in our most recent experience, are listed in Tables 6 and 7.

Intestinal Amebiasis

1. *Asyndromic amebiasis*, the most frequent form of the disease, may be subdivided into 2 descriptive phases: (a) carrier state, or asymptomatic cyst passer, and (b) latent amebiasis.

(a) *Carrier state*, or asymptomatic cyst passer, represents a phase of infection in which the host-parasite relation is assumed to permit *E. histolytica* to be harbored as a harmless commensal. Our observations do not substantiate correlation of such vague complaints as malaise, asthenia, anorexia, headache, functional dyspepsia and emotional disturbances of "toxemia" with the presence of *E. histolytica* cysts in the stool. Through suggestions, some physicians, on "discovering" the "cause" of an illness, have created iatrogenic disease or dependency of patients on an antiamebic program. When

TABLE 7.—CLINICAL COURSE OF SYMPTOMATIC AMEBIASIS
(5-Year Follow-up Study of 100 Consecutive Cases)

Diognostic Classification	Rendered Asymptomatic "cured" E. Histolytica Eradicated	Persistent Infection	Complications	Total no. of cases
Asyndromic (latent amebiasis)	60	5	5*	70
Amebic Colitis				
Acute	6			6
Chronic	17	1	2**	20
Hepatitis	2			2
Hepatic Abscess	1		1***	2
Total	86	6	8	100

*3 hepatic, 2 granuloma. **1 hepatic, 1 granuloma.
***Pleurobronchial fistula.

such patients eventually come under the care of other physicians, *E. histolytica* is not demonstrable, even though the symptoms remain. Carriers have no significant roentgenographic or proctoscopic findings, and their stools are guaiac-negative.

(b) *Latent amebiasis* is characterized by such minor enterocolonic complaints as gastrocolic reflex, flatulence, distention, transient diarrhea (often precipitated by dietary or alcoholic indiscretions), tenesmus, urgency of defecation, abdominal soreness, malaise and fatigue, in association with demonstrable *E. histolytica* in the feces. These patients respond symptomatically to eradication of the parasite and

remain well after successful therapy. Many (23.1% of 52 patients) have roentgenographic evidence of colonic hyperirritability, primarily involving the cecum and suggestive of amebic cecitis (5). The stools are often guaiac-positive. Occasionally, typical minute amebic ulcers are visible on proctosigmoidoscopic examination (7.3% of 109 cases) (5).

In view of these observations, as well as the experiences of others with amebic complications, including fatalities in patients with asyndromic and latent amebiasis, these forms of the disease should be considered as entities that deserve adequate therapy.

2. *Amebic colitis* is a phase of amebiasis in which diarrhea of varying severity is accompanied by significant abdominal discomfort and either or both roentgenographic and endoscopic evidence of amebic ulceration. This condition simulates all other forms of colonic ulcerative disease in which stools contain blood, mucus and pus.

(a) *Acute amebic colitis* varies in severity of symptoms from mild tenesmus to severe fulminating febrile dysentery. Typically, the onset is rather insidious, with mild, but progressive, symptoms. Similar acute or moderate-to-severe episodes may recur. Spontaneous "cures," simulating an asyndromic latent phase, may take place without treatment. Fever is fairly common with the acute and severe bouts of illness (16.4% of 77 cases) (5) but rarely accompanies mild and chronic illness unless secondary infection is a complicating factor.

Abdominal, colic-like pain, with intense tenesmus, is associated with defecation. If it is localized at the site of involvement, this region will be exquisitely tender. The most prominent constitutional symptoms, which vary with the severity of the disease, degree of dehydration and loss of blood, are malaise, anorexia and extreme weakness after defecation. Fulminating cases, which may result from progression of milder complaints, are manifested by fever, toxicity, leukocytosis, loss of blood and depletion of fluids and electrolytes. In our survey, death from either or both exsanguination and perforation occasionally (0.36% of cases) preceded therapy, which had not been instituted because of diagnostic error.

(b) *Chronic amebic colitis* is characterized by intermittent or constant diarrhea, alternating with constipation. Loss of

weight, lassitude, anemia and colonic irritability are common. Abdominal tenderness, roentgenographic evidence of mucosal change (41.3% of 141 cases) and proctoscopically demonstrable ulceration (54.1% of 133 cases) are to be expected (5). These manifestations, in our experience, have often been erroneously diagnosed as (idiopathic) ulcerative colitis when the patient has failed to respond to inadequate amebacidal therapy. The possible coexistence of (idiopathic) ulcerative colitis and malignant disease of the colon should never be overlooked.

Diarrheic stools may be identified by their primarily fecal content, as contrasted with the cellular debris of dysenteric stools. To the practical observer, then, most patients have one or more diarrheic stools daily and a varying number of fluid or dysenteric stools, with additional defecation of globs of mucosanguinous material. A specific foul, musty odor has been ascribed to amebic stools by astute observers.

3. *Perforation of the colon* is reported more frequently in areas in which the more fulminating phases of amebiasis are encountered. In our statistical survey, we encountered only one such instance. The clinical picture in such catastrophes is that of acute severe peritonitis with shock. Occasionally, perforation occurs where localization is possible; abscess or formation of fistula will result unless prompt drainage and specific therapy are exacted.

4. *Amebic granulomas,* tumefactions of the intestinal wall for which the term ameboma has been coined, are the result of a granulomatous fibrous tissue reaction to repeated amebic invasion with secondary infection. Ulceration involves the mucosal surface; small abscesses and amebic burrows characterize the infiltrate. Sloughing results in a deep necrotic ulcer. These granulomas may simulate neoplastic involvement, in partial obstruction alternating with diarrhea and secondary inflammatory reaction. Biopsy, when the lesion is endoscopically available, and favorable response to emetine hydrochloride are diagnostic aids when the presence of *E. histolytica* in the stool does not conclusively exclude a neoplasm or granuloma of other etiology.

5. *Colonic strictures,* from prolonged or recurrent infection, may result in obstructive phenomena.

6. *Pseudopolypoid or true polypoid changes* have occurred in association with amebiasis.

1. *Amebic hepatic disease* has been divided into 2 phases of involvement: (a) hepatitis (presuppurative) and (b) hepatic abscess (suppurative).

(a) *Hepatitis.*—Clinical skill in differentiating the tenderness in the right abdominal region as primarily hepatic, along with observation of diminution in hepatic enlargement after antiamebic therapy, may suggest hepatic disease states in patients with otherwise asyndromic amebiasis. It is certainly conceivable that hepatitis, without true abscess formation or with multiple miliary abscesses, may be a precursor of the coalescence of minute foci which creates a true amebic hepatic abscess. We are reluctant to concede that the frequency of hepatitis concomitant with amebiasis is as great as has been assumed without confirmatory pathologic data.

"Chronic amebic hepatitis" has been described in *E. histolytica* cyst passers who manifest fatigue, anorexia, right abdominal discomfort and perhaps hepatic enlargement and tenderness. Lack of therapeutic response and absence of confirmatory histologic data render the existence of such an entity doubtful.

(b) *Amebic hepatic abscess*, which is more prevalent in male patients (8:1), should be suspected in any such patient with unexplained chills and fever, hepatic discomfort or pain, with tenderness localized over the liver or tenth rib, moderate leukocytosis and loss of weight. An unusual cafe' au lait appearance of the skin is characteristic. Right diaphragmatic distortion is confirmatory; involvement of the lower portion of the liver, however, may result in colonic or gastric pressure defects rather than diaphragmatic changes. *E. histolytica* may or may not be demonstrable on fecal study. Response to emetine hydrochloride or chloroquine diphosphate, alone or in combination, supports the diagnosis (Fig. 16). Aspiration of a chocolate brown cellular detritus from an abscess is diagnostic, and demonstration of *E. histolytica* is pathognomonic. Occasionally, an abscess may perforate spontaneously to create a cutaneous sinus, a hepatobronchial fistula with fetid suppurative sputum, pneumonitis and pleuritis, or free peritonitis and force the unsuspecting to the diagnosis.

It is most important to remember that amebic hepatic abscess often exists without symptoms referable to amebic

colonic involvement. Furthermore, onset is often insidious, with mild symptoms persisting for some time prior to development of the suppurative stage. Interesting diagnostic features include relief of pain when the patient lies on the left side, cecal tenderness, shock percussion tenderness over the right tenth rib in the posterior axillary area and right basal pulmonary changes.

2. *Amebic appendicitis* may be suspected clinically when acute right lower abdominal manifestations develop in a patient known to have amebiasis. Appendiceal involvement is usually an extension of amebic cecitis. Although considered the most frequent surgical complication of amebiasis (7 to 40% of cases) (6), it was recognized in only 0.75% of cases in our survey. The impression of subacute and chronic

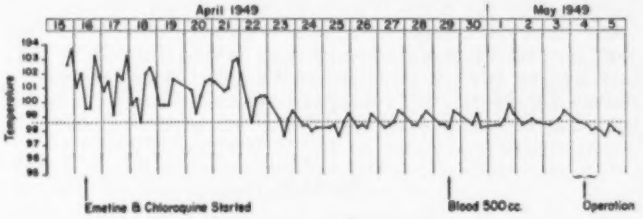


FIG. 16.

appendicitis is rarely gained on histologic study, although appendectomies have been performed rather frequently in patients with amebiasis and suspected appendicitis. Appendectomy, when the result of diagnostic error, is hazardous because of the associated cecitis and tendency of the closure to perforate and precipitate postappendectomy peritonitis or fistula.

3. *Cutaneous amebiasis* should be suspected when a sinus occurs spontaneously or is induced at a site of visceral extension. Such a sinus usually results from an underlying abscess (hepatic, appendiceal, colonic or perianal) in a patient suspected of, or known to have, amebiasis. Primary cutaneous involvement is rare. The cutaneous lesion is characterized by irregular, overhanging, necrotic, ulcerated, edematous margins surrounded by an area of cyanotic, reddened skin. Refractory to local therapy, the lesions extend, and

scarring is widespread. The discharge is sanguinopurulent and of musty, foul odor. *E. histolytica* can be identified in the tissues.

4. *Miscellaneous amebic disorders* are:

(a) *Metastatic abscesses* to the brain, spleen, lung, kidney or elsewhere are occasionally found in severe cases of amebiasis. Localizing symptoms depend on the area of involvement.

(b) *Genitourinary affections*, involving the genitalia by direct extension from anal lesions or abscesses, have been the subject of individual case reports and, obviously, will be suspected only if symptoms indicate invasion of such sites.

The potentialities of amebic infection (Tables 6 and 7) should warn against complacency, which is easily assumed because of the "curative" response of most patients (85 to 90%) (25) to well-conducted therapy, the spontaneous "cure" of a reasonable number of patients (16%) (21) and the rarity of intractable or recurring cases (7 to 10%). Reinfection may explain some instances reported as recurrent or intractable. Significant complications are encountered in less than 3% of cyst passers and 7% of symptomatic cases.

THERAPY

Intestinal Amebiasis

1. *Asyndromic or asymptomatic cyst passer.*—This person, a public health menace and potential symptomatic patient, should be treated adequately, although the intensive regimen often exacted is not essential. We have found 3 consecutive 10-day courses of one of the intestinal amebacides, as outlined for acute amebic colitis, to be curative.

2. *Amebic Colitis.*—(a) *Acute.* Therapeutic measures proved to be effective should be instituted as soon as a diagnosis of amebiasis is made (13-25). The following steps, which have proved effective, should be followed in the treatment of patients infected with *E. histolytica* when the specific type of involvement is recognized (16-18, 21, 24, 25-28).

First 10 days:

1. Erythromycin stearate, 200 mg., or oxytetracycline, 500 mg., every 6 hours for 10 days.
2. Simultaneous administration of Carbarsone®, 0.75 Gm. daily, glycobiarsol (Milibis®), 1.5 Gm. daily, diiodohydroxyquin (Diodoquin®), 1.9 Gm. daily, or Balarsen®, up to 500 mg. daily for 5 days.

Second 10 days:

Choice of: Fumagillin (Fumidil®), 60 mg. daily, or Carbarsone®, glycobiarson, or diiodohydroxyquin for 10 days. (Drugs used during first 10 days should not be repeated, preferably.)

Third 10 days:

Any of the foregoing nonantibiotic drugs, at the same schedule stipulated, but none previously used to be repeated, preferably.

Supportive measures should be instituted in the acute stages of the disease, as required by the individual case, such as administration of parenteral fluids, dietary restriction to minimize residue of either liquids or soft food, replacement of blood when necessary, and institution of antidiarrheal measures, including administration of bismuth, kaolin, sedatives and opiates. Emetine hydrochloride, 60 mg. subcutaneously daily for a maximum of 10 days, is indicated only if diarrhea cannot be controlled by antidiarrheal measures.

The acute stage may be spontaneously reversible. When the diagnosis is correct, cure may be expected in almost all cases, since the deep tissues have not been invaded. In the occasional intractable case, the program outlined should be repeated with daily administration of 1.0 Gm. of chloroquine diphosphate for 20 days. Achievement of a "cure" may be determined by a follow-up examination with 3 fecal studies at 30-day intervals.

(b) *Chronic.* The therapeutic program for chronic amebic colitis consists of incorporation of the three 10-day schedules outlined for acute amebic dysentery with administration of chloroquine diphosphate, 1.0 Gm. daily, during 20 of the 30 days of treatment. When the organism persists after this course of therapy, the entire schedule should be repeated, emetine being added during the second 10 days. Because of the cytotoxic action of this drug, bed rest, with control electrocardiograms, is imperative during its administration. If symptoms recur, the initial 30-day program should be repeated. After completion of therapy, fecal examinations should be made at 30-day intervals for at least 6 months.

3. *The Defunctionalized Colon with Amebiasis.*—We have not observed adequate colonic concentration of antiamebic agents by oral or parenteral routes but have obtained successful results with combined proximal and distal colonic instillation of Carbarsone® and Diodoquin® alternately for 10 days each.

4. *Amebic Granuloma.*—Amebacides usually effect a dra-

matic response in patients with amebic granuloma, but not always so, and sometimes a questionable deformity remains. A healthy anastomotic site is usually produced by proper preoperative preparation of the intestinal tract with oxytetracycline when granuloma is suspected. Preoperative use of emetine may increase the operative risk. Postoperative amebacidal therapy is the same as that for chronic amebic colitis.

Extraintestinal Amebiasis

Hepatitis, hepatic abscess, pleuritis, draining sinuses, peritonitis and peritoneal abscesses should receive the same intensive therapeutic program outlined for chronic amebic colitis. Emetine and chloroquine are the specifics in such instances with the other agents as adjuncts. It may sometimes be necessary to irrigate abscesses with emetine hydrochloride, followed by drainage.

1. *Appendicitis.*—The risk of appendectomy is increased by the presence of an unhealthy, leaking appendiceal stump. Parenteral use of oxytetracycline, and erythromycin is advocated and even administration of emetine is justified by the severity of the condition.

2. *Abscess.*—When hepatic and subphrenic abscesses do not subside with adequate therapy and closed drainage, operative drainage may be necessary. Every therapeutic ingenuity, including operation, may be needed in the management of parasitemia, with bizarre metastases to the brain, genitourinary tract and other sites.

3. *Amebiasis cutis.*—Treatment described for asyndromic or asymptomatic amebiasis may be employed for this condition, when the diagnosis is presumed. Whereas emetine hydrochloride has been accredited with cure of cutaneous amebic disturbances, its efficacy cannot be proved, since the diagnosis is often simply presumed, without confirmatory histopathologic changes.

4. *Surgical intervention in amebiasis.*—The indications for operation have been comprehensively reviewed in other publications (8, 9, 36, 39).

5. *Prophylactic administration of amebacides.*—For persons who plan to enter areas in which water and food supplies or food handlers are known to transmit amebiasis, prophylaxis may be needed. Most amebacides are not sufficiently innocuous to be safe for such use. Diodoquin® has

the fewest side effects and, in our experience, *E. histolytica* has not been demonstrable in the stools of treated patients on their return from areas in which the incidence of amebiasis was high.

CONTROL

The pathogenicity of amebiasis suggests modes of prophylaxis. Man himself is responsible for the maintenance of this public health problem throughout the world. The Public Health Service should exact control of migratory populations, food handlers, sewage disposal and sanitary measures in order to eliminate insect carriers. In institutions or heavily infected areas, chemotherapeutic measures should be exercised to eliminate this disease. An educational program to emphasize the importance of personal hygiene and good sanitation should be incorporated in the program of control, so that major periodic epidemics, which still occur, may be prevented.

SUMMARY AND CONCLUSIONS

Infection with *Entamoeba histolytica* is an important clinical problem because of its incidence and potentially severe variations. The geographic distribution, pathogenesis and clinical manifestations of the various forms of amebiasis and its complications are described, including laboratory findings, proctoscopic signs and roentgenographic features, and the importance of accurate diagnosis and early, adequate therapy is emphasized. An effective therapeutic regimen for various amebic states is outlined.

The wide spectrum antibiotic drugs have the following actions as intestinal amebacides: (1) amebic inanition, by disturbance in bacterial flora, (2) control of secondary infection, (3) nullification of invasive bacterial aid to the amebae and (4) direct amebacidal action. Of the antibacterial antibiotic agents, erythromycin and oxytetracycline are the best conditioning agents or true amebacides. Fumagillin is an extremely effective amebacide of the restricted bacterial spectrum antibiotic drugs.

Amebic photography was accomplished with the advice and assistance of Dr. Francis Spencer of San Angelo Medical and Surgical Clinic, and Dr. Lee Monroe of Scripps Clinic and Research Foundation.

Art work and composition was completed by Don Alvarado, Department of Medical Illustration, LSU School of Medicine.

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